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Identification of MiRNAs associated with radioresistance in a prostate cancer model

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Purpose/Objective: High risk of tumour regrowth following treatment with radiation therapy for a subset of prostate cancer patients highlights the need for prognostic biomarkers. miRNAs are key regulators of cancer cell behavior that could control their response to ionizing radiation. Owing to their availability in tissues, serum and urine, miRNAs are ideal candidates for the development of novel biological tests. This study aimed to identify key miRNAs associated with a radioresistant phenotype in cancer cells, as a prerequisite for the future development of a novel pre-treatment assay for the identification of radiotherapy prostate cancer patients at risk of biochemical failure.

Materials and Methods: A dual approach was used for the identification of candidate miRNAs associated with radioresistance: (1) an isogenic radiation resistant model was generated using the 22Rv1 (primary) prostate cancer (CaP) cell line through weekly exposure to 2-Gy fractionated ionising radiation. (2) chronically hypoxic 22Rv1 cells (48hrs) were used as an additional model for radioresistance. miRNA profiling of radioresistant and wild type cells was performed using the Exiqon miRCURY array and overlapping differentially expressed miRs were identified.

Results: Following a cumulative total dose of 60Gy, the radiation survival curve of the resulting subline RR22Rv1 was associated with a significant increase in clonogenic survival (1.3 fold increase in survival after 2Gy and 2.2 fold increase after 10Gy), when compared to both parent 22Rv1 and age-matched controls. The RR22Rv1 cell line is associated with decreased sensitivity to DNA damage (comet assay), enlargement of the S-phase cell population (PI staining) but no evidence for expansion of the senescent cell fraction (B-Gal assay). miRNA profiling identified 105 significantly differentially expressed miRNAs in RR22Rv1, when compared to the parent and age-matched control 22Rv1 cells. A total of 12 miRNA were differentially expressed in chronically hypoxic compared to normoxic 22Rv1 cells. Three candidate miRNAs were associated with a radioresistant phenotype across the models: miR200a, miR210 and miR4284. Functional validation of these candidates is currently under way.

Conclusions: This study demonstrates a role for miRNAs in the radioresponse of prostate cancer cells and highlights their potential for the development of novel prognostic biomarkers for radiotherapy prostate cancer patients.

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Image analysis for enhancing the bladder-prostate junction on radiotherapy planning CT images

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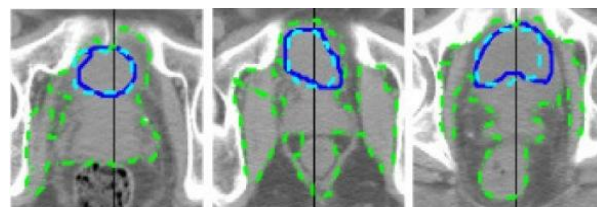
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Purpose/Objective: Organ preservation of muscle invasive bladder cancer after external radiotherapy is an important outcome for those patients who are unresectable or chose not to have cystectomy. Geometric uncertainties due to pelvic organ movement and internal bladder motion present a major challenge in defining the true extent of the bladder on computerised tomography (CT) images. This is complicated further by a lack of soft tissue contrast on CT images at the bladder prostate junction (BPJ) where significant clinical experience is required to interpret and ensure that the dose to the prostate remains within acceptable limits. The aim of this study was to investigate the use of image analysis for enhancing the BPJ on CT images used for RT planning and thereby allow simple image thresholding to produce reliable estimates of the clinical target volume (CTV). This has application in adaptive radiotherapy for automatically defining the bladder volume on cone-beam CT (CBCT).

Materials and Methods: Image data was acquired on a single slice General Electric (GE) HiSpeed Fx/i CT scanner (GE Medical Systems, Milwaukee, WI, USA) with 0.977 mm pixel resolution in the transaxial plane and a 2048 grey-level range. Five bladder cancer patients treated with a radiation dose of 52.5 Gy (20 fractions/4 weeks) at the Edinburgh Cancer Centre (ECC), were included in this study. Each patient received a 3 mm thick CT scan, with a presumed empty bladder, which was used to: define the target volume; define critical anatomical structures; determine the optimum radiation beam arrangement; and estimate the dose. Where possible CT scanning was performed twice weekly and repeat CT scans registered against bone on the corresponding planning scan using the GE Advantage fusion software. This resulted in 36 data sets, which were contoured by an experienced radiation oncologist and image analysis methods used to produce a new image set containing the enhanced BPJ.

Results:



On the 36 new data sets a threshold was set to extract the CTV, which included the bladder and BPJ. The variability

($\mu\pm\sigma$) of the volume identified by image analysis on the new image sets and by an experienced oncologist on the original image sets was 0.76 ± 0.13 measured by the Dice similarity criterion (DSC). 17 cases had a DSC above 0.8; 17 cases had a DSC between 0.8 and 0.6; 2 cases had a DSC below 0.6. The figure shows the CT images from three bladder cancer patients. The Blue contour is the CTV; green is the CTV produced by thresholding of the original CT images; cyan is the CTV produced by thresholding of the image analysis enhanced CT image, which shows good agreement with the clinical contours using the BPJ-enhanced image data. Conclusions: The image analysis study presented for defining the CTV on low contrast CT images has the potential to be used as part of an adaptive radiotherapy system. Such a simple approach was not possible on the original image set. Although good agreement was found between the clinical and image analysis defined CTV this study serves only to provide pilot results. More extensive validation is required using CBCT and more observers.

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Hypofractionated split course radiotherapy for elderly patients with prostate cancer and comorbidities

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Purpose/Objective: Treatment of prostate cancer in frail elderly patients is challenging. Many of such patients are not candidates for surgery, brachytherapy or SBRT. Conventionally fractionated radiotherapy is frequently a choice, but duration of such treatment appears as an apparent challenge for frail individuals. To address these problems we designed a hypofractionated split course radiation therapy (HSC-RT) that, potentially, allows treatment in reduced number of fractions without compromising effectiveness. Because prostate cancer does not repopulate rapidly split course RT was allowed. Planned interruption may reduce acute reactions and may facilitate comfortable outpatient management of patients.

Materials and Methods: Elderly frail patients with intermediate or high risk prostate cancer were considered as candidates for the present study. Radiation dose of 62,5 Gy in 2.5 Gy per fraction was given over 9 weeks with two planned gaps of 14 days each, after accumulation of 25 Gy and 50 Gy. Median age of the patients in the analyzed pilot series of 20 patients was 76 years (range 67-83), most patients had impaired general performance (ZUBROD 1-2). A series of 130 consecutive patients (comparable risk characteristics, good PS, median age of 67 years) treated with conventionally fractionated radiotherapy (dose of 70-76 Gy, median 74 Gy) was used for comparison of biochemical outcome. Neoadjuvant ADT was used in both groups. PSA concentration and treatment tolerance was assessed at follow-up.

Results: In general, HSC-RT was well tolerated, (the highest RTOG score for bladder toxicity during treatment was 1 for

45% of patients, 2 for 15%, 3 for 5%, rectal toxicity was minimal with highest score 1 in 15 % of patients. There were not late rectal toxicity and late bladder toxicity was minima with highest score 1). Baseline median pretreatment PSA concentration was the same in both groups (15 ng/ml). However, in spite of planned treatment gaps, the PSA measurements at follow-up revealed somewhat favorable biochemical outcome in patients treated with HSC-RT, compared to those treated conventionally (CF). Median PSA concentration (ng/ml) at follow-up was lower in HSC-RT compared to CF (0.03 vs. 0.08 at 12 months; 0.03 vs. 0.13 at 24 months; 0.01 vs. 0.22 at 36 months). Median PSA nadir was 0.013 ng/ml for HSC-RT vs. 0,03 for CF.

Conclusions: While the results of this study are limited by a small size and clinical heterogeneity of the analyzed group the outcome presented suggest that hypofractionated split course radiation therapy in frail elderly patients with intermediate/high risk prostate cancer is feasible and does not compromise biochemical control.

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Clinical outcomes of image guided adaptive radiotherapy (IGART) for hypofractionated treatment of bladder cancer

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Purpose/Objective: Anatomical variation in bladder position and size has driven on-line IGART strategies to prevent geographical misses. A 'plan of the day' IGART approach improves target coverage and reduces normal tissue irradiation. We report on the clinical outcomes of patients treated in a phase 2 study with hypofractionated radiotherapy using this technique.

Materials and Methods: Fifty-five patients with T2-T4aN0-2 M0 bladder cancer not suitable for cystectomy or daily radiotherapy treatment were recruited between February 2009 and March 2014. A library of 3 plans were created (using small, medium and large PTV) from planning CT scans performed at 0 and 30 minutes, treating whole (empty) bladder to 36Gy in 6 weekly fractions. Cone beam CT (CBCT) imaging was performed prior to each fraction. Appropriate PTV was selected from the library for treatment delivery. Acute toxicity was assessed weekly during radiotherapy and at 6 and 12 weeks using CTCAE v3.0. Late toxicity was assessed at 6 months and 12 months using Radiation Therapy Oncology Group (RTOG) grading. Local control was assessed at 3 months preferentially with cystoscopy, or if this was not possible with imaging alone (CT/MRI). Local progression free